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Regulatory Proposal PRO2016-03

Essential Oil-based Personal Insect Repellents (EOPIR)

Information Requirements for Assessment of Risks to Human Health

Addendum to the Guidelines for the Registration of Non-Conventional Pest Control Products (DIR2012-01)

(publié aussi en français)

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1.0 Introduction

On 27 February 2012, Health Canada's Pest Management Regulatory Agency (PMRA) published Regulatory Directive DIR2012-01 *Guidelines for the Registration of Non-Conventional Pest Control Products*. This directive outlined a flexible risk-based regulatory approach for assessing whether non-conventional pest control products have value and whether they represent any unacceptable risks to human health or the environment. DIR2012-01 includes criteria for determining whether products are eligible for review under the directive, and information required for product chemistry, the assessment of risk to human health, the assessment of risk to the environment, and the assessment of value. DIR2012-01 also includes a discussion of the submission process including presubmission consultation and the submission of information for regulatory decision making.

The purpose of this Regulatory Proposal is to consult on proposed regulatory requirements for the assessment of risk to human health for a specific type of non-conventional pest control product, essential oil-based personal insect repellents (EOPIR).[1] Essential oils are complex mixtures of volatile compounds produced as secondary metabolites in aromatic plants. They can be extracted from these plants by distillation, solvent extraction, cold pressing, and other means. In this case, the qualifier "essential" means that the oils contain the characteristic fragrance of the plants from which they were extracted. Examples of essential oils include clove oil, tea tree oil, lemon oil, and camphor oil. Essential oils and their components have a wide range of applications including in medicinal agents, cosmetics/perfumes, food flavourings, natural health products, and pesticides.

While DIR2012-01 includes a tiered approach to information requirements for assessing the risks to human health for non-conventional pest control products, the nature of the exposure to EOPIRs differs from other non-conventional pesticides as they can be applied directly to human skin and label directions often provide for repeated applications over the course of a day. These unique exposure characteristics and PMRA's previous experience with the assessment and registration of personal insect repellents containing essential oils such as oil of lemon eucalyptus led the Agency to conduct a review of the applicability of the existing tiered approach to information requirements for EOPIRs and whether an alternative approach should be considered. On 3 December 2014, Health Canada announced the review to all stakeholders by publishing an information note, which included the Department's commitment to engage with an external advisory panel prior to publishing the proposed requirements for public consultation.[2]

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1 Personal insect repellents are substances that are applied to clothing or directly to human skin in order to repel or deter insects from landing and/or biting. Most repellents form a vapour barrier that causes the insect to avoid the skin surface. A number of essential oils have been found to have these properties and have been registered as active ingredients in commercially available insect repellents in Canada, the United States, and other countries.

2 Review of the Regulatory Approach for Personal Insect Repellents Containing Plant-Derived Essential Oils 3 December 2014 (Information Note) http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_fact-fiche/essential_oils-huiles_essentielles/index-eng.php

While the other elements of DIR2012-01 will continue to apply to EOPIRs, the information requirements in this addendum, once finalized, will supersede the information required for the assessment of risks to human health from exposure to EOPIRs as outlined in DIR2012-01. In other words, the scope of this addendum is limited to the information requirements for conducting a health risk assessment for EOPIRs.

The PMRA invites the public to submit written comments up to 60 days from the publication of this regulatory proposal. Please forward all comments to PMRA Publications. (Contact information can be found on the cover page of this document.)

2.0 Essential Oil-based Personal Insect Repellent External Advisory Panel (EOPIR EAP)

A key component of PMRA's review of the applicability of the existing tiered approach to information requirements to EOPIRs was a consultation with an external advisory panel (EAP), which was held on 6 January 2016. The EAP was composed of scientific experts in this field and the reporting structure/governance of the EAP was based on guidance provided in *Health Canada's Policy on External Advisory Bodies* (2011).[3]

The mandate of the EAP included providing confirmation that the existing tiered approach to information requirements for non-conventional pest control products could be applied to EOPIRs. Input was also sought on approaches to assessing potential data gaps either through the tiered approach described in DIR2012-01 or an alternative approach recommended by the advisory panel. The EAP was asked to provide PMRA with guidance on the following:

- The acceptability of the current tiered approach to information requirements for assessing health risks of EOPIRs.
- The acceptability of using such a tiered approach to address the uncertainty and data gaps in the database for a previously registered pest control product, citronella oil.

The *Final Report of the Essential Oil-based Personal Insect Repellent External Advisory Panel (EOPIR EAP)* can be found on the Essential Oil-based Personal Insect Repellent External Advisory Panel webpage in the Pesticides and Pest Management portion of Health Canada's website. A summary of the charge questions posed to the EAP, the EAP's recommendations relating to each charge question, and PMRA's responses to the EAP recommendations is included as Appendix I to the final report.

As mentioned in the December 2014 Information Note, while PMRA's review of the approach to information requirements for EOPIRs is being conducted, including the consultation period for this regulatory proposal, currently registered personal insect repellents containing plant-derived essential oils will be permitted to remain on the market for sale and use.

While the scope of this review and consultation does not include a consideration of methyleugenol, a naturally occurring constituent of some essential oils, Section 4.0 of this

[3] http://www.hc-sc.gc.ca/ahc-asc/public-consult/res-centre/poli-eab-oce-eng.php

document provides background information on the compound and the concentration limit established for it in EOPIRs by PMRA. This section supplements the information on methyleugenol provided in the 2014 Information Note, which indicates that for personal insect repellents containing citronella oil specifically, only those products which have met the allowable concentration limit for the constituent of concern (methyleugenol) may remain on the market for sale and use during this time.

3.0 EOPIR Tiered Information Requirements

One of the components of the registration process is an assessment to ensure that an EOPIR will not pose any unacceptable risks to human health. In order to conduct this type of assessment, PMRA requires applicants and registrants to submit information on the toxicity and exposure to the EOPIR. Similar to the assessment of all non-conventional pest control products, PMRA recognizes that regulatory information requirements and decisions for EOPIRs should be commensurate with the level of anticipated risks. Consequently, PMRA has proposed a tiered approach to toxicity and exposure information requirements for EOPIRs that is derived from the tiered approach for non-conventional pest control products but incorporates a number of specific modifications recommended by the EAP. Similar to other non-conventional pest control products, higher-tier information will be required if the potential for adverse effects is observed from the results of the lower-tier information.

Information requirements are designated as either "required" or "conditionally required". Conditionally required means that the information is only required under specific conditions such as the potential for exposure by multiple routes, specific use patterns, and higher-tier toxicology and exposure information requirements triggered by effects observed in lower-tier studies. More information on the conditions is provided in the footnotes to the tables accompanying the descriptions of the toxicology and exposure information requirements in Sections 3.1 and 3.4, respectively.

Sources of data to address information requirements for EOPIRs can include the results of unpublished or published studies, regulatory reviews conducted in other countries, and published literature reviews. In some cases, information requirements may be waived based on scientifically valid rationales. More information on waiver rationales for toxicology information for EOPIRs is provided in Section 3.2.

When considering original testing, applicants and registrants are encouraged to consult PMRA on proposed protocols before initiating any studies. This is particularly important when proposed protocols deviate from internationally recognized testing guidelines.

Applicants and registrants must provide sufficient information to support a regulatory decision and are encouraged to make use of the PMRA pre-submission consultation process described in Section 3.1 of DIR2012-01 if they require guidance on information requirements for EOPIRs.

3.1 Toxicology Information Requirements

Toxicology information is required to assess the hazards of EOPIRs to human health. Toxicology information is also considered along with information on exposure when conducting human health risk assessments of EOPIRs. Toxicology information submitted for EOPIR technical grade active ingredients and end-use products must be sufficient to demonstrate that they pose low risks to human health following acute and repeated exposures. For technical grade active ingredients and end-use products, Tier I toxicology information requirements include information on acute toxicity, as well as short-term toxicity, reproductive toxicity, and developmental toxicity (combined repeated dose and reproductive/developmental toxicity screening test).

If adverse effects are observed for endpoints in any of the Tier I toxicology studies for the technical grade active ingredient, then additional endpoint-specific information may be required at Tier II.

If adverse effects are observed in any of the Tier II toxicology studies for the technical grade active ingredient, the EOPIR may be re-profiled as a conventional pesticide and conventional pesticide toxicology and exposure information requirements for personal insect type use patterns (in other words, Use Site Category (USC) 26 – Human Skin, Clothing, and Proximal Sites) may be required.

More detail on the tiered toxicology information requirements for EOPIR technical grade active ingredients and end-use products can be found in Tables 1 and 2, respectively.

Table 1 Toxicology Information Requirements for EOPIR Technical Grade Active Ingredients

Data Code (DACO)	OECD / USEPA Guideline Number	Information Requirement	Required / Conditionally required	Test Notes
TIER I				
ACUTE TOXICITY STUDIES				
4.2.1	420, 423, 425 / 870.1100	Acute oral toxicity	Required	1
4.2.2	402 / 870.1200	Acute dermal toxicity	Required	2
4.2.3	403, 436 / 870.1300	Acute inhalation toxicity	Required	1, 3
4.2.4	405 / 870.2400	Primary eye irritation	Required	4
4.2.5	404 / 870.2500	Primary dermal irritation	Required	4
4.2.6	406, 429, 442A, 442B / 870.2600	Dermal sensitization	Required	5
4.2.9	n/a	Other acute studies	Conditionally required	6
SHORT-TERM/REPRODUCTIVE/DEVELOPMENTAL TOXICITY STUDIES				
4.8	422 / 870.3650	Combined repeated dose and reproductive/developmental toxicity screening test	Required	1, 7
GENOTOXICITY TESTING (IN VITRO)				
4.5.4	471 / 870.5100	Genotoxicity: Bacterial reverse mutation assay	Required	8
4.5.5	476 / 870.5300	Genotoxicity: In vitro Mammalian cell assay	Required	9
SPECIAL STUDIES				
4.8	n/a	Other studies/Data/Reports	Conditionally required	6

Data Code (DACO)	OECD / USEPA Guideline Number	Information Requirement	Required / Conditionally required	Test Notes
TIER II[10]				
SHORT-TERM TOXICITY STUDIES				
4.3.1	408 / 870.3100	Short-term oral toxicity (90 day rodent)	Conditionally required	1, 11, 12
4.3.4	411 / 870.3250	Short-term dermal toxicity (90 day rodent)	Conditionally required	1, 11
4.3.6	413 / 870.3465	Short-term inhalation (90 day rodent)	Conditionally required	1, 13
4.3.8	n/a	Other short-term studies	Conditionally required	6
REPRODUCTIVE/DEVELOPMENTAL TOXICITY				
4.5.1	416, 443/ 870.3700, 870.3800	Reproduction, fertility, and developmental Effects	Conditionally required	1, 14, 15
GENOTOXICITY TESTING (IN VIVO CYTOGENETICS)				
4.5.7	475 / 870.5385	Mammalian bone marrow chromosomal aberrations	Conditionally required	16
	474 / 870.5395	Mammalian erythrocyte micronucleus	Conditionally required	16
SPECIAL STUDIES				
4.3.8	n/a / 880.3550	Immunotoxicity	Conditionally required	17

OECD = Organisation for Economic Co-operation and Development; USEPA = United States Environmental Protection Agency

[1] The preferred species is the rat.

[2] The preferred species is the rat or rabbit.

[3] Required if the test substance, under conditions of use, will result in a respirable material (for example, vapour, aerosol or particulate).

[4] The preferred species is the rabbit.

[5] For the Guinea Pig Maximisation Test and the Buehler Test, the preferred species is the guinea pig.

[6] Other available studies that elaborate on the toxicity profile of a test substance.

[7] Administration by oral intubation is preferred.

[8] Additional mutagenicity tests that may have been performed plus a complete reference list (and a copy of each reference) must also be submitted. Subsequent testing may be required based on the available evidence.

[9] This includes choice of assay using the mouse lymphoma L5178Y cells, thymidine kinase (tk) gene locus, maximizing assay conditions for small colony expression and detection; Chinese hamster ovary (CHO) or Chinese hamster lung fibroblast (V79) cells, hypoxanthine-guanine phosphoribosyl transferase (HGPRT) gene locus; or CHO cell strain AS52, xanthine-guanine phosphoribosyl transferase (XPRT) gene locus.

[10] If adverse effects are observed in any of the Tier II toxicology studies, the substance would be re-profiled as a conventional pesticide and conventional pesticide toxicology and exposure information requirements for Use Site Category 26 (Human skin, clothing, and proximal sites) may be required.

[11] Required if adverse effects (other than reproductive or developmental effects) are observed in the Tier I combined repeated dose and reproductive/developmental toxicity screening test.

[12] The incorporation of a post-treatment recovery phase should be considered.

[13] Required if adverse effects (other than reproductive or developmental effects) are observed in the Tier I combined repeated dose and reproductive/developmental toxicity screening test, and if there is a likelihood of significant levels of repeated inhalation exposure to the pesticide as a vapour, aerosol or particulate.

[14] Required if there is evidence of adverse reproductive, developmental or endocrinological effects from the Tier I combined repeated dose and reproductive/developmental toxicity screening test, or evidence of potential genotoxicity to mammals based on the results from the Tier I mutagenicity tests.

[15] This includes a choice of a two-generation rat reproductive toxicity study and a rat prenatal developmental toxicity study, both conducted by the oral route of exposure or a one-generation reproductive toxicity study with developmental toxicity endpoints conducted by the dermal route of exposure. A study of dermal dosing tolerance may be necessary to ensure that it is possible to conduct the main study without having to remove animals due to skin irritation.

[16] Required if results from the Tier I mutagenicity tests are positive. Assays using rodent bone marrow, using either metaphase analysis (aberrations) or a micronucleus assay, are preferred.

[17] Required if there are effects on hematology, clinical chemistry, lymphoid organ weights and histopathology observed in the Tier I combined repeated dose and reproductive/developmental toxicity screening test or in the Tier II short-term toxicity studies.

n/a = none available

Table 2 Toxicology Information Requirements for EOPIR End-use Products

Data Code (DACO)	OECD / USEPA Guideline No.	Information Requirement	Required / Conditionally required	Test Notes
TIER I				
ACUTE TOXICITY STUDIES				
4.6.1	420, 423, 425/ 870.1100	Acute oral toxicity	Required	1
4.6.2	402/ 870.1200	Acute dermal toxicity	Required	2
4.6.3	403, 436/ 870.1300	Acute inhalation toxicity	Required	1, 3
4.6.4	405/ 870.2400	Primary eye irritation	Required	4
4.6.5	404/ 870.2500	Primary dermal irritation	Required	4
4.6.6	406, 429, 442A, 442B/ 870.2600	Dermal sensitization	Required	5
4.6.8	n/a	Other acute studies	Conditionally required	6
SHORT-TERM/REPRODUCTIVE/DEVELOPMENTAL TOXICITY STUDIES				
4.8	422 / 870.3650	Combined repeated dose and reproductive/developmental toxicity screening test	Conditionally required	1, 7, 8
4.7.7	n/a	Other short-term studies	Conditionally required	8, 9
SPECIAL STUDIES				
4.8	n/a	Other studies/Data/Reports	Conditionally required	6

OECD = Organisation for Economic Co-operation and Development; USEPA = United States Environmental Protection Agency

[1] The preferred species is the rat.

[2] The preferred species is the rat or rabbit.

[3] Required if the test substance consists of, or if under conditions of use will result in, a respirable material (for example, vapour, aerosol or particulate).

[4] The preferred species is the rabbit.

[5] For the Guinea Pig Maximisation Test and the Buehler Test, the preferred species is the guinea pig.

[6] Other available studies that elaborate on the toxicity profile of a test substance.

[7] Administration by oral intubation is preferred.

[8] This may be required if any component of the end-use product may increase absorption of the active ingredient(s) or increase the toxic or pharmacological effects.

[9] This may include other available studies of shorter duration such as range-finding studies that elaborate on the toxicity profile of the test substance.

n/a = none available

3.2 Rationales to Waive Toxicity Testing

In some cases specific toxicology information requirements for an EOPIR may be waived based on a scientifically valid rationale. A weight of evidence approach should be used to develop waiver rationales, including a consideration of multiple lines of evidence. Examples of types of evidence used in waiver rationales for toxicity information requirements for EOPIRs could include the following:

- History of non-pesticidal uses with similar use patterns/exposure levels to the proposed personal insect repellent use, such as:
    - Information on the history of the use of the EOPIR active ingredient as an approved ingredient in cosmetics, personal care products, natural health products, and other products with similar use patterns/exposure levels to the proposed use.
    - Information on the extent to which the proposed personal insect repellent use will increase exposure to the active ingredient above existing non-pesticidal uses.

- Extensive searches of the published scientific literature demonstrating no evidence of toxicity and/or no adverse effects for the EOPIR active ingredient and any metabolites.
- Published toxicology data for individual components of the active ingredient with an accompanying rationale for why this surrogate data should be considered as representative of the expected toxicological effects for the whole active ingredient. If no published empirical toxicology data are available, data generated for the components of the active ingredient from alternative approaches may be considered (for example, read-across, (quantitative) structure activity relationships [(Q)SAR]).
- Information on proposed label uses that may reduce or limit human exposure, for example:
    - Label statements limiting the number of daily applications of the EOPIR, advising that the EOPIR not be used under clothing or on children under 2 years of age, etc.

Waiver rationales must include all relevant supporting information (for example, regulatory reviews from other countries, published scientific studies, material safety data sheets,).

PMRA has developed guidance and criteria specific to the waiving of acute toxicity data, as well as the extrapolation of data from one product to another (that is, bridging data). Applicants and registrants are encouraged to consult the PMRA guidance document, *Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides*[4] and the Organisation for Economic Cooperation and Development document *Guidance Document on Considerations for Waiving or Bridging of Mammalian Acute Toxicity Tests Series on Testing & Assessment No. 237*,[5] when preparing rationales to waive acute toxicity testing for EOPIRs.

3.3 In Vitro Alternative Testing

The development and application of in vitro alternative toxicity testing methods is one component of an overall international effort to incorporate 21st century toxicology and integrated approaches to testing and assessment (IATA) into regulatory risk assessment. The PMRA is currently contributing to a number of national and international initiatives to investigate the scientific validation and application of various in vitro alternative testing methods to regulatory information requirements for pest control products. A consideration of alternative approaches also formed part of the discussion with the EOPIR EAP on approaches to information requirements for EOPIRs.

Recognizing that the science continues to emerge and work is on-going in this area, PMRA will consider for review waiver rationales based on weight of evidence approaches that include the results of validated, internationally accepted in vitro alternative toxicity tests.

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4 http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/toxicity-guide-toxicite/index-eng.php

5 http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

3.4 Exposure Information Requirements

Tier I information required to assess exposure to EOPIRs includes the draft labels for the technical grade active ingredients and end-use products, as well as information on the proposed use patterns. The required information can include the locations on the body or clothing where the EOPIR is applied, the method of application (lotion applied by hand, pump spray, etc.), the amount of EOPIR applied to the body, the number of applications per day, any contraindications on the use (for example, do not spray on face, do not use on damaged skin, or do not use on children under age 2), and any potential for bystander exposure during application of the product. Information on the dermal absorption of EOPIRs is also required and can include in vitro study data, preferably combined with information on physical-chemical properties and/or other sources of information in a weight of evidence approach. Alternatively, data from triple-pack studies (in other words, in vivo animal, in vitro animal, and in vitro human) may be submitted.

If any of the submitted Tier I toxicology data indicate that an EOPIR may pose a potential hazard to the user, more extensive Tier II exposure data may be required.

More detail on the tiered exposure information requirements for EOPIR end-use products can be found in Table 3.

Table 3 Exposure Information Requirements for EOPIR End-use Products

Data Code (DACO)	USEPA Guideline No.	Information Requirement	Required / Conditionally required	Test Notes
	TIER I			
5.2	875.1700	Use description scenario	Required	1
5.8	428 / 870.7600	Dermal absorption study	Required	2, 3, 4
	TIER II			
5.7	875.2400, 875.2500, 875.2600	Biological monitoring	Conditionally required	5, 6
5.10	875.2400, 875.2500, 875.2600	Ambient air samples	Conditionally required	5, 7, 8
5.14	n/a	Other Studies/Data/Reports	Conditionally required	5

[1] Information that fully describes the proposed use of the product(s) and the human activity associated with its use should be submitted. Information should include, but not necessarily be limited to the following: sites of application (for example, skin and/or clothing), method of application (for example, apply lotion by hand, pump spray, etc.), approximate amount to be applied to skin and/or clothing, maximum number of applications per day, contraindications or limitations on use (for example, do not spray on face, do not apply under clothing, do not apply on injured skin, do not use on children under two years of age, etc.)

[2] This can include in vitro study data, preferably combined with physical-chemical property information and/or other sources of information (for example, information on the dermal absorption potential of components of the active ingredient, information on the dermal absorption of surrogates, etc.) in a weight of evidence approach. Alternatively, data from triple-pack studies (in other words, in vivo animal, in vitro animal, and in vitro human) may be submitted.

[3] In vitro studies should be performed using viable skin and a flow-through apparatus.

[4] In vivo animal studies are usually conducted on rodents.

[5] These data are required when any toxicology data in Tables 1 or 2 indicate that the EOPIR may pose a potential hazard to the user. Applicants are advised to consult PMRA prior to study initiation to determine what studies are appropriate based on the nature of the adverse effects seen in the toxicology studies and the available exposure data. Studies performed to support the registration of EOPIRs may require modifications to existing guidelines.

[6] Surrogate data may be acceptable if the toxicokinetics are well understood for the purposes of converting internal to external dose.

[7] Required if there is a potential for post-application inhalation exposure.

[8] Breathing zone samples are preferred.

n/a = none available

4.0 Methyleugenol

As mentioned above, the scope of this review and consultation does not include methyleugenol; however, the intent of this section is to include information that supplements what is currently provided on Health Canada's web site, which includes the information related to methyleugenol that is provided in the December 2014 information note.[6]

Methyleugenol is a natural constituent of essential oils derived from several different plant species. The naturally occurring concentration of methyleugenol varies with the plant variety, stage of plant maturity at harvest, method of harvesting, storage conditions, and method used to extract the essential oil.

In the proposed acceptability for continuing registration document, PACR2004-36 *Re-evaluation of Citronella Oil and Related Active Compounds for Use as Personal Insect Repellents*, PMRA stated that methyleugenol has been demonstrated to be a genotoxic carcinogen in rats and mice and noted the conclusion of the United States National Toxicology Program that methyleugenol is "reasonably anticipated to be a human carcinogen". PMRA also adopted the European Commission's conclusion that the concentration of methyleugenol in cosmetic products "may not exceed ... 0.0002% in other leave on product..." as applicable to personal insect repellents.

Consequently for EOPIRs known to contain methyleugenol, analyses must be provided to show that the level of methyleugenol present in the end-use product is less than 0.0002% (2 ppm).

5.0 Next Steps

The PMRA invites the public to submit written comments on this proposal up to 60 days from publication. Please forward all comments to PMRA Publications. The PMRA will consider all comments received before making a final decision. Please note that submitted comments should be limited to those relating to the toxicology and exposure information requirements for EOPIRs discussed in this proposal. Comments are not being solicited on the EAP process or the Panel's report, the PMRA's concentration limit for methyleugenol in EOPIRs or on previously published information requirements for citronella oil in personal insect repellents.

Please provide your comments and include the following information: your full name and organization, telephone number, and complete mailing address or e-mail address.

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[6] Review of the Regulatory Approach for Personal Insect Repellents Containing Plant-Derived Essential Oils 3 December 2014 (Information Note) http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_fact-fiche/essential_oils-huiles_essentielles/index-eng.php